glomerular cells] control element comprises a cytomegalovirus enhancer and a chicken beta-actin promoter.

Please add new claims 13-17:

13. The method according to claim 1, wherein said gene encodes Green Fluorescence Protein

14. The method according to claim 1, wherein said gene encodes Erythropoetin.

15. The method according to claim 1, wherein said gene encodes CD-2-Associated Protein;

16. The method according to claim 1, wherein said gene encodes Nephrin.

17. An animal model for testing the efficacy and efficiency of the transfer of a viral vector carrying one or more genes into the renal glomerular cells of said animal under conditions such that neither the left kidney nor the liver are exposed to said gene-carrying vector, comprising an animal in which the right kidney, the aorta and the right renal blood vessels are exposed, the aorta is clamped above and below the right renal artery and the SMA, the vector is infused into said right kidney by means of a needle inserted in said SMA or renal artery, said right kidney is cooled to minimize ischemia, renal circulation is reestablished after the infusion period, and gene transfer efficiency is determined by staining tissue sections for expression of the transferred gene, said model being depicted in Fig. 1.

REMARKS

Claims 1-12 were pending in the application. All claims have been rejected. The applicants respectfully request reconsideration of the rejections in the light of the above-shown claim amendments, new claims, Rule 132 Declarations from two experts, and the following remarks.

Oath/Declaration

The examiner continues to object to the form of the declaration of inventorship originally filed 10/10/2001. Therefore, new declarations are enclosed.

Claim Rejections- 35 *USC IOI*

Claims 1-12 have been rejected on a nine-page allegation that the claimed invention is not supported by a specific, substantial and well-established utility. The chief thrust of the examiner's arguments is that it is the Office's position that gene therapy is not yet a credible, established technique. These rejections are traversed.

The applicants maintain that, although gene therapy of renal diseases is a goal sought by many, this is not the subject of the claimed invention. The utility of the present invention lies in the creation of an animal (mammalian) model for the evaluation of the efficacy and efficiency of gene vectors and other agents to be used for treating renal glomerular diseases. This is stated clearly in the specification.

The examiner is respectfully referred to paragraph [011] where it is stated:

"The present invention provides the first demonstration of efficient gene transfer into rat renal glomerular cells without inducing significant glomerular injury. It is a simple method that can be used to create small animal models to study the effect of foreign gene

transfer into renal glomeruli." (Emphasis added)
In addition, paragraph [015] states in the first line:

"To produce a rodent animal model..."

Finally, in the last line of the Abstract on page 18, it is stated:

"The invention can be used for both *in vitro* and *in vivo* applications in...laboratory animal models."

The applicants submit that these quotations from the specification demonstrate very clearly that their invention has at least one specific, substantial and credible utility that would have been recognized by one of skill in the art at the time that the application was filed. This is all that is required by the Guidelines (Utility Examination Guidelines, Federal Register 66(4), Jan. 5,2001), upon which the examiner bases his rejection, to satisfy 35 USC 101.

Claim 1 has now been amended, and claim 18 added, to clarify these points.

To demonstrate that those of average skill in this art would have considered the claimed invention specific, substantial and credible at the time that the present patent application was filed, the applicants submit Abstracts from two publications of the inventors: (1) Ye *et al.* Efficient Gene Transfer In Rat Renal Glomeruli With Recombinant Vectors, *Human Gene Therapy* 12: 141-148 (Jan. 20, 2001); and (2) Ye *et al.* (same title as above), *Pediatric Research* 4 Part 2: 421A (May 1, 2001). As these are peer-reviewed journals, it follows that those of

average skills in this art found the invention to be specific, substantial and credible.

The aforementioned Guidelines also provide (see, p. 1098, col. 2, first paragraph) for the submission of affidavits or declarations from experts in the art to demonstrate that one of ordinary skill in this art would have considered the inventive animal model credible for the avowed purpose at the time of the filing of applicants' patent application. To this end, the applicants submit a declaration and *curriculum vitae* from Mark L. Batshaw, MD, who is an expert on the needs for and values of test animal models for renal diseases, including future gene therapies; references 67-70, 74, 83 and 85 are particularly important in this regard. The applicants also submit a declaration from Kurt Newman, MD, who is an expert on surgical techniques, including those used to produce the inventive model. These declarations establish clearly that the claimed animal model had specific, substantial and credible utility at the time of the filing of the patent application.

The applicants respectfully request that the examiner withdraws the utility rejections.

Claim Rejections-35 USC 112 *(first paragraph)*

The examiner couples his views under 35 USC 101 with the requirements of 35 USC 112 (first paragraph) to reject all pending claims on the basis of non-enablement, asserting that the applicants have not demonstrated credible utility of gene therapy involving renal glomerular diseases. The applicants traverse these rejections.

The examiner is respectfully referred to their utility arguments *supra.* The applicants have established that they have described in detail and claimed an animal model that can be used to test the efficacy and efficiency of candidate

drugs, including vector-gene constructs, in transferring these agents into renal glomerular cells, for the ultimate treatment of disease. They have established that this is a specific, substantial and credible utility that would be recognized as such by those of average skill in this art. Applicants need only a single such utility to traverse a rejection under 35 USC 101, according to the aforementioned Guidelines. Therefore, as the 35 USC 101 underpinnings of the rejections have been successfully traversed, rejections under Section 112 should also be withdrawn.

Rejection of Claim 2 under 35 USC 112 (first paragraph)

Claim 2 has been rejected on an assertion that it is too broad in view of the use of the words "preferentially expresses" in connection with the control elements disclosed by the specification. The examiner is quite correct in stating that the CMV enhancer and chicken beta action promoter confer constitutive gene expression in any particular cell type (see p. 12, last paragraph of the current Office Action, paper 9). In keeping with the examiner's correction, claim 1 has been amended to refer to <u>any</u> control element that <u>allows</u> gene expression. Along the same vein, claim 2 has been amended to recite a specific control element. The applicants submit that, at the time this application was filed, it was generally known in the field that several ubiquitous promoters worked in glomerular cells.

The examiner is respectfully requested to withdraw this rejection.

New claims

The applicants have added five new claims, all of which are fully supported in paragraphs [014], [015] and [016] of the specification, and original claim 1

("gene or genes of interest").

Previous withdrawals of rejections

The applicants acknowledge with appreciation the withdrawal by the examiner of his previous rejections under 35 USC 112 (second paragraph) and 35 USC 102(b).

Conclusion

All claims are deemed by the applicants to be allowable. Accordingly, the examineris respectfully requested to withdraw all objections and rejections, and pass this application to issue.

Respectfully submitted,

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MARKED UP COPY OF AMENDED CLAIMS

1. A method of [infecting] transferring into the glomerular cells of a kidney of a model [mammalian subject] mammal [with] a [recombinant adenovirus vector carrying a] gene or genes of interest, comprising the step of infusing intra-renal arterially and continuously in a single pass through the superior mesenteric artery ("SMA") or renal artery an effective amount of [said adenoviral vector] a recombinant adenovirus vector carrying said gene or genes of interest into said kidney at an effectively slow rate over an effective period of time, under conditions such that at least 30% of said glomerular cells are infected with said vector, wherein said adenovirus vector carries a control element that allows expression of said gene or genes or interest in renal glomerular cells.

2. The method according to claim 1, wherein said [adenovirus vector carries a control element that preferentially expresses said gene or genes into renal glomerular cells] control element comprises a cytomegalovirus enhancer and a chicken beta-actin promoter.